REMARKS

The specification and claim 19 are amended herein by including chemical names for the following compounds: "FK228 (FR901228)"; "NVP-LAQ824 ((2E) -N-hydroxy--3- [4- ({ (2-hydroxyethyl) [2- (1H-indol-3yl)ethyl]amino)methyl)phenyl]acrylamide)"; "Apicidin (cycle(N-O--methy-L-tryptophanyl-L-isoleuciny-D-pipecolinylL-2--amino-8-oxodecanoyl)"; "CI-994 (N-acetyldinaline)"; and "CHAP (cyclic hydroxyamio acid containing peptides)." No new matter is presented.

I. Evidence and Information Disclosure Statement

The Office Action indicates that the references included in Applicants' Appeal Brief filed October 27, 2008 were not considered as not being properly cited on an Information Disclosure Statement. Applicants presume the Office Action refers to references submitted with the Amendments filed November 27, 2006 and January 31, 2008 and listed in the Evidence Appendix of the Appeal Brief filed October 3, 2008. In this regard, Applicants note that the Examiner is incorrect and these references do not have to be cited in an IDS in order to be "entered and considered as evidence". Applicants refer to MPEP § 609.05(c), which provides:

> To the extent that a document is submitted as evidence directed to an issue of patentability raised in an Office action, and the evidence is timely presented, applicant need not satisfy the requirements of 37 C.F.R. §1.97 and 37 C.F.R. §1.98 in order to have the examiner consider the information contained in the document relied on by applicant. In other words, compliance with the information disclosure rules is not a threshold requirement to have information considered when submitted by applicant to support an argument being made in a reply to an Office action.

The Office Action also states that 'partial translations' should be provided with the complete reference, or portion thereof, and a complete citation. To this end, Applicants note that partial English translations were submitted with the reference or relevant portion thereof. Specifically in the Evidence Appendix at page 17 of the Appeal Brief, item (3) refers to "Partial English translation of New Integrated Medical Lectures..." submitted as Reference Document 3 with the Amendment filed November 27, 2006 and both the partial English translation and the relevant portion of the reference were provided and labeled as "Document 3" and "Reference Document 3," respectively. Similarly, item (4) refers to "Partial English translation of Orthopedic Surgery..." submitted as Reference Document 4 with the Amendment filed November 27, 2006 and both the English translation and the reference document were provided and labeled as "Document 4" and "Reference Document 4," respectively.

In view of the above, Applicants submit that the literature references referred to above and in the Appeal Brief were properly submitted as "evidence" and should have been entered and considered by the Examiner at the time they were submitted. Applicants further submit that the Examiner's failure to enter and consider the evidence as such is improper and even if the

evidence was not properly submitted, the issue should have been raised at the time of submission and not after the filing of an Appeal Brief relying on such evidence.

Applicants also do not understand what the Examiner means by the statement, "evidence includes citation of the reference cited in the rejection." Clarification is respectfully requested.

II. Response to the Objection to the Specification and Claim 19

The Office Action objects to the specification and claim 19 as reciting various HDAC inhibitors by their 'common name', e.g. CHAP, FK228, etc and not defined in the specification, or in the claim.

Applicants respectfully traverse the objection. In this regard, Applicants submit that it is not improper to recite to the "common name" of compounds in the specification or the claims as long as the "common name" properly identifies a particular compound and the meaning is well-known and satisfactorily defined in the literature. See MPEP § 608.01(v)[1].

Applicants submit that one skilled in the art can recognize the compounds mentioned in the specification and in claim 19 by common names because the compounds have been reported with the common names recited in the specification before the present invention was filed as their meanings are well known and satisfactorily defined in the literature. Furthermore, except

[1] MPEP § 608.01(v) states: "Names used in trade are permissible in patent applications if: (A) Their meanings are established by an accompanying definition which is sufficiently precise and definite to be made a part of a claim, or (B) In this country, their meanings are well-known and satisfactorily defined in the literature." "Names in trade" are defined as "a nonproprietary name by which an article or product is known and called *among* traders or *workers in the art*, although it may not be so known by the public, generally. Names used in trade do not point to the product of one producer, but *they identify a single article or product* irrespective of producer."

for some of the compounds, the structures of the compounds are disclosed on page 19 of the specification.

Regarding the remaining compounds, Applicants submit a review article on the HDAC inhibitor, TRENDS in Endocrinology & Metabolism 12(7), 294-300, 2001 ("Reference 1")[2], to establish the recognized meaning of the common names recited in the specification and claim 19 at the time the present application was filed.

Notwithstanding the above, the specification and claim 19 are amended by adding chemical names of some compounds which are not so frequently reported as HDAC inhibitors compared to the other compounds.

Accordingly, Applicants respectfully request withdrawal of the objection to the specification and to claim 19 which states:

III. Response to Claim Rejections under 35 U.S.C. § 102

A. Chung

The Office Action indicates that claims 18-21 are rejected under 35 U.S.C. § 102(e) as being anticipated by Chung (US 2005/0245439 A1; "Chung").

Applicants respectfully traverse the rejection.

Chung is a publication of an application which is a continuation-in-part (CIP) of Ser. No. 10/132,999, filed on April 26, 2002. Chung may therefore only be applied as prior art under 35

[2] Reference 1 is properly submitted as evidence in support of Applicants' argument in reply to an Office Action, thus an Information Disclosure Statement is not necessary for its consideration. See MPEP § 609.05(c).

U.S.C. § 102(e) for subject matter commonly disclosed in the parent '999 application filed on April 26, 2002. However, the parent '999 application does not describe a method of treating osteoarthritis as in the '439 publication of Chung. The '999 application primarily relates to a composition and method for the treatment of inflammation of skin, joints and soft tissues due to altered patterns of immunoregulation such as rheumatoid arthritis, systemic lupus, erythematosus, progressive systemic sclerosis, sjorgen's syndrome, dermatomyositis and mixed tissue disease (see paragraph [0002] of the published '999 application, Pub. No. 2003/0206946). The '999 parent application does not describe or enable the presently claimed method of treating osteoarthritis, which is not an immunoregulated disease.

Moreover, based on the finding that an HDAC-inhibiting compound has an inhibitory activity on articular cartilage extracellular matrix degradation, the present invention provides a pharmaceutical effective for treating osteoarthritis involving articular cartilage extracellular matrix degradation. On the other hand, '999 application neither discloses nor suggests that an HDAC inhibiting compound has an inhibitory activity on articular extracellular matrix degeneration.

Therefore, the '999 application does not adequately support, enable or describe a method of treating osteoarthritis. The earliest effective prior art date of the Chung '439 publication is March 14, 2005, which is after the effective date of the present application of August 19, 2003, based on the prior filed International Application. Therefore, subject matter disclosed in the '439 publication which is not disclosed or supported by the '999 application cannot be relied on as prior art to the present application.

Accordingly, Applicants respectfully request withdrawal of the § 102 anticipation rejection based on Chung.

B. Watkins

The Office Action indicates that claims 18-21 are rejected under 35 U.S.C. § 102(e) as being anticipated by Watkins (WO 02/30879 A2; "Watkins").

Applicants respectfully traverse the rejection and submit that Watkins does not contain an enabling disclosure and therefore the present invention is not anticipated.

The Examiner indicates that the instant specification states that HDACi's have been used for treatment of rheumatoid arthritis and osteoarthritis. Applicants note that this was previously addressed in the Amendment filed June 6, 2008 (see pages 8-9), in which Applicants pointed out that the Examiner's interpretation of this portion of the disclosure of the present specification is incorrect as follows:

> Specifically, at page 6 of the instant specification it is disclosed that a number of diseases are cited in patent reference 1, including rheumatic arthritis and osteoarthritis, but no specific effect is described and the basis which indicates a therapeutic effect is not shown. That is, the reference is not enabling for rheumatic arthritis and osteoarthritis. See the paragraph bridging pages 6-7 of the specification. Additionally, in the specification of patent reference 1, for the FK228 reduced form, a number of diseases are cited for the reason that the FK228 reduced form is effective for diseases induced by abnormal gene expression by its HDAC-inhibitory activity. Therein, although rheumatic arthritis and osteoarthritis are cited, any specific effect is not described and the basis which indicates a therapeutic effect is not shown. Thus, it is clear that the description in the present specification at page 6 referred to by the Examiner is to explain that the patent reference 1 is not enabling for rheumatic arthritis and osteoarthritis even though these conditions are mentioned therein.

At page 9, the Office Action indicates that Applicants admit that treatment of osteoarthritis with an HDACi was known in the present specification in teaching that hyaluronic acid was known only as a symptomatic treatment of alleviating pain involved in cartilage degeneration and subchondral bone destruction at page 7 of the specification. In this regard, the Examiner asserts that hyaluronic acid is an HDACi.

However, Applicants respectfully disagree with the assertion that hyaluronic acid is classified as an HDACi. First, Applicants note that hyaluronic acid is not described as an HDACi in the present specification. To this end, Applicants submit Arthritis Rheum., 43:1905, 2000 ("Reference 2")[3] as a reference which describes the principles of osteoarthritis treatments. In the reference, hyaluronan is included in the pharmaceuticals that are used for treating osteoarthritic patients, as shown in Table 3 on page 1909. Although the results of the treatments of intraarticular hyaluronan are described in the third paragraph on page 1910, it is not described that hyaluronan is an HDACi. The Examiner has not provided a reasonable basis for asserting that hyaluronic acid is an HDACi. Thus, Applicants respectfully disagree with the Examiner's assertion that hyaluronic acid is an HDACi. The Examiner is respectfully requested to provide evidence in support of the conclusion that hyaluronic acid is an HDACi.

At pages 5-6 of the Action, the Examiner states that the rejection is based on Watkins and not in view of Takahashi or Dangond and that there is no express or implicit statement by

[3] Reference 2 is properly submitted as evidence in support of Applicants' argument in reply to an Office Action, thus an Information Disclosure Statement is not necessary for its consideration. See MPEP § 609.05(c).

Watkins or in Watkins that Takahashi and/or Dangond are the basis for teaching that HDACi's are useful for treating osteoarthritis. This is another point which was previously addressed in the Amendment filed June 6, 2008. Specifically, Applicants pointed out that the proper standard for evaluating a reference:

> A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art. In considering the disclosure of a reference, it is proper to take into account not only specific teachings of the reference but also the inferences which one skilled in the art would reasonably be expected to draw therefrom. In this regard, it is apparent to one skilled in the art that the references Dangond and Takahashi are citations as support for the foregoing description in Watkins at page 111, lines 1-2, so that these two references should be taken into consideration: "Inflammatory disease (e.g., osteoarthritis, rheumatoid arthritis) (see, e.g., Dangond et al., 1998; Takahashi et al., 1996)." When viewed in the proper context, one skilled in the art would understand from the word "see" that the references cited are for reference and thus the findings relating to "inflammatory disease, osteoarthritis, rheumatoid arthritis" are described in the references cited after the word "see". Thus, it is clear that Watkins cites the Dangond and Takahashi references in support of the assertion that HDAC inhibitors were known to be useful in the treatment of inflammatory disease such as osteoarthritis. Otherwise, there would be no need to specifically cite these references separate from the other references cited in support of other conditions mentioned in the disclosure of Watkins.

The majority of the Examiner's other points are sufficiently addressed in the Appeal Brief. For instance, at page 6 of the Action, the Examiner maintains that Watkins classifies both rheumatoid arthritis and osteoarthritis as inflammatory and not autoimmune diseases. However, Applicants have already pointed out that this statement is contrary to the knowledge and skill in the art with respect to treatment of osteoarthritis and therefore, Watkins cannot serve as an

enabling disclosure. See Appeal Brief filed October 30, 2008, pages 9-12, incorporated herein by reference.

The Office Action further indicates that Applicants have not provided facts sufficient to rebut the presumption that Watkins is operable for the treatment of osteoarthritis. To this point and in addition to the above presented arguments, Applicants reiterate the following: (1) the disclosure of Watkins is directed to inhibition of proliferative conditions, such as cancer and psoriasis and that the biological activity concretely disclosed in Watkins is merely a finding of "the ability to inhibit deacetylase activity and to inhibit cell proliferation" (cf. pages 230-247); (2) Watkins provides no example of treatment of osteoarthritis; (3) the only mention of the osteoarthritis is at pages 110-111 of the reference; (4) the knowledge and remainder of the prior art does not support the description in the Watkins reference that it was well known that HDACi's could be used for the treatment of osteoarthritis; (5) Watkins refers to osteoarthritis as an inflammatory disease but that this statement was contrary to the knowledge in the art at the time as shown by Reference Documents 3 and 4 and their partial English translations properly submitted as evidence with the Amendment filed November 27, 2006; (6) Dangond et al and Takahashi et al, which are cited in Watkins as references for inflammatory disease (e.g., osteoarthritis, rheumatoid arthritis), describe that the immunosuppressive activity is the base and each of these references indicates that the HDAC inhibitor acts on rheumatoid arthritis through immunosuppressive activity; (7) osteoarthritis is not an autoimmune disease as evidenced by Reference Documents 3 and 4 mentioned above; (8) even if Watkins could be considered as describing osteoarthritis and rheumatoid arthritis in parallel, one skilled in the art who

understood the contents of all of these references would not consider that the HDAC inhibitor can act on osteoarthritis through its immunosuppressive activity and rather would doubt its enablement; and (9) there is no other reference of record which supports the Examiner's position that Watkins undoubtedly teaches that HDACi's were known to be useful for the treatment of osteoarthritis. In view of the foregoing arguments, Applicants respectfully submit that sufficient facts have been provided to rebut the Examiner's position indicated in the Office Action.

The Examiner's statements regarding the person of ordinary skill in the art are not seen as particularly relevant since the Examiner refers to standards and cases relating to obviousness and the present rejection is an anticipation rejection. For example, MPEP § 2141.03 is a subsection under §2141 entitled "Standards and Guidelines for Determining Obviousness under 35 U.S.C. § 103" and *KSR v. Teleflex* refers to the person of ordinary skill in the art being able to fit the teachings of multiple patents together like pieces of a puzzle", wherein the Examiner is relying on a single reference and has not provided any other references which supports the assertions made in the reference relied on. The question is whether the claimed invention was in possession of the public prior to the effective date of the present application and not whether one of ordinary skill in the could have put together multiple references to arrive at the claimed invention. Applicants' position is that the teachings in the reference relied on by the Examiner as teaching how to make and use the claimed invention of treating osteoarthritis are insufficient, not supported by the knowledge and skill available in the art, and subject to doubt by those of ordinary skill in the art at the time of the present invention.

Finally, in response to the Examiner's assertion that Chung '439 also provides that HDACi's were known for treating osteoarthritis, Applicants note that, as stated above, Chung '439 is not prior art to the present application for the disclosure that is not commonly described in the parent '999 application and the disclosure of the parent '999 application does not mention osteoarthritis. Therefore, Chung '439 does not rebut Applicants' position that, as of the effective date of present application, HDACi's were not known to be useful for the treatment of osteoarthritis.

Applicants submit that the '999 application of Chung actually supports Applicants position regarding the knowledge in the art at the time of the present invention. Specifically, paragraph [0002] of the '999 application, cited by the Examiner, states: "[m]ore particularly, the present invention relates to a pharmaceutical composition and method for the treatment of inflammation of skin, joints and soft tissues due to altered patterns of immunoregulation such as rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, sjogren's syndrome, dermatomyositis and mixed connective tissue disease." Thus, the '999 application demonstrates that when the present application was filed, HDAC-inhibiting compound was considered to be effective for treating inflammation of skin, joints and soft tissues, which are caused by immune abnormalities.

As shown in pages 6-7 of the instant specification, it was known at the time the present application was filed that "an HDAC inhibitor can be used for the treatment of autoimmune diseases on the basis of the fact that the HDAC-inhibitor exhibits an effect of normalizing abnormal expression of immune-related genes in T cells collected from patients of systemic

lupus erythematosus." Accordingly, one skilled in the art would have recognized that an HDAC inhibitor has an activity to both normalize the immunity and treat inflammatory diseases induced by abnormal immunity based on the effects of normalizing abnormal expression of immune-related genes in T cells.

On the other hand, osteoarthritis is explained in the first paragraph on page 1905 of Reference 2. In the last sentence of the reference paragraph, the pathogenesis of osteoarthritis is described as follows: "biomechanical stresses affecting the articular cartilage and subchondral bone, biochemical changes in articular cartilage and synovial membrane, and genetic factors are all important in its pathogenesis." Therefore, one skilled in the art would have considered that osteoarthritis is not an immune-relating disease.

Aside from Watkins, the Examiner has not indicated any reference that describes osteoarthritis as a subject disease of an HDACi prior to the present invention. One skilled in the art cannot simply would not have expected that an HDACi is effective for osteoarthritis based on the above recognition, particularly in view of the Watkins disclosure. As addressed, Watkins does not support using an HDACi for treating osteoarthritis, and therefore does not contain an enabling disclosure for using an HDACi for treating osteoarthritis.

As to Examiner's assertion that Chung also indicates that HDACi's were known for treating osteoarthritis, Applicants reiterate that the subject matter disclosed in Chung '439, which is not supported by the '999 parent application is not prior art to the present application. Therefore, since the treatment of osteoarthritis as disclosed in the '439 publication is not supported by the parent '999 application, Chung does not rebut Applicants' position that as of

the effective date of present application, HDACi's were not known to be useful for the treatment of osteoarthritis.

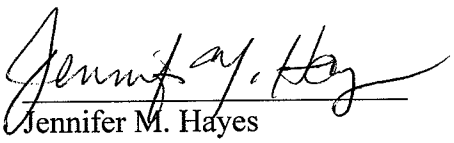
Accordingly, Applicants respectfully request withdrawal of the § 102 anticipation rejection based on Watkins.

IV. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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